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Ohki , et al. **May 15, 2001**

Cyclic hexapeptides with antimicrobial activity

Abstract

This invention relates to new polypeptide compounds represented by general formula (I), wherein R.sup.1, R.sup.2, R.sup.3 and R.sup.4 are as defined in the description or a salt thereof which has antimicrobial activities (especially, antifungal activities), inhibitory activity on .beta.-1,3-glucan synthase, to process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal. ##STR1##

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Claims

What is claimed is:

1. A polypeptide compound of following the general formula: ##STR607##

wherein

R.sup.1 is hydrogen;

arylamino (lower) alkanoyl which may have one or more substituent(s);

aroyl substituted with heterocyclic group which may have one or more substituent(s);

aroyl substituted with aryl having higher alkyl;

aroyl substituted with aryl having lower alkyl;

aryl (C.sub.2 -C.sub.6) alkanoyl substituted with aryl having lower alkyl;

lower alkanoyl substituted with unsaturated condensed heterocyclic group which may have one or more substituent(s);

lower alkanoyl substituted with pyridyl which may have one or more substituent(s);

heptylnaphthoyl;

hexylnaphthoyl;

aroyl substituted with heterocyclic carbamoyl which may have one or more substituent(s);

lower alkanoyl substituted with cyclo (lower) alkyl which may have one or more substituent(s);

lower alkanoyl substituted with thienyl having heterocyclic group which may have one or more substituent(s); or

lower alkanoyl substituted with heterocyclic group which may have one or more substituent(s),

R.sup.2 is hydrogen or hydroxy,

R.sup.3 is hydroxy, hydroxysulfonyloxy or lower alkoxy, and

R.sup.4 is hydroxy or lower alkoxy, or a salt thereof.

2. A compound of claim 1, wherein

R.sup.1 is aroyl substituted with heterocyclic group which may have one or more substituent(s).

3. A compound of claim 2, wherein

R.sup.1 is benzoyl substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) having phenyl which has a substituent selected from the group consisting of saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have cyclo (lower) alkyl having di (lower) alkyl, lower alkoxy (lower) alkoxy, lower alkoxy (higher) alkoxy and phenyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) having di(lower) alkyl; or benzoyl substituted with unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) having phenyl which has lower alkoxy.

4. A compound of claim 3, wherein

R.sup.1 is benzoyl substituted with thiadiazolyl which has phenyl having piperidyl,

benzoyl substituted with thiadiazolyl which has phenyl having lower alkoxy (lower) alkoxy,

benzoyl substituted with thiadiazolyl which has phenyl having lower alkoxy (higher) alkoxy,

benzoyl substituted with thiadiazolyl having phenyl which has piperazinyl substituted with cyclohexyl,

benzoyl substituted with thiadiazolyl having phenyl substituted with phenyl which has morpholino having di (lower) alkyl, or

benzoyl substituted with imidazothiadiazolyl having phenyl which has lower alkoxy.

5. A compound of claim 4, wherein

R.sup.1 is benzoyl substituted with thiadiazolyl which has phenyl having piperidyl, or benzoyl substituted with thiadiazolyl which has phenyl having lower alkoxy (higher) alkoxy,

R.sup.3 is hydroxysulfonyloxy, and

R.sup.4 is hydroxy.

6. A process for preparing a polypeptide compound of claim 1 or a salt thereof, which comprises,

i) reacting a compound of the formula: ##STR608##

wherein

R.sup.2, R.sup.3 and R.sup.4 are as defined in claim 1 or its reactive derivative at the amino group or a salt thereof, with a compound of the formula:

R.sub.a.sup.1 --OH

wherein

R.sub.a.sup.1 is arylamino (lower) alkanoyl which may have one or more substituent(s);

aroyl substituted with heterocyclic group which may have one or more substituent(s);

aroyl substituted with aryl having higher alkyl;

aroyl substituted with aryl having lower alkyl;

aryl (C.sub.2 -C.sub.6) alkanoyl substituted with aryl having lower alkyl;

lower alkanoyl substituted with unsaturated condensed heterocyclic group which may have one or more substituent(s);

lower alkanoyl substituted with pyridyl which may have one or more substituent(s);

heptylnaphthoyl;

hexylnaphthoyl;

aroyl substituted with heterocyclic carbamoyl which may have one or more substituent(s);

lower alkanoyl substituted with cyclo (lower) alkyl which may have one or more substituent(s);

lower alkanoyl substituted with thienyl having heterocyclic group which may have one or more substituent(s); or

lower alkenoyl substituted with heterocyclic group which may have one or more substituent(s),

or its reactive derivative at the carboxy group or a salt thereof, to give a compound of the formula:

##STR609##

wherein

R.sup.2, R.sub.3 and R.sup.4 are as defined in claim 1, and

R.sub.a.sup.1 is as defined above or a salt thereof, or

ii) reducing a compound of the formula: ##STR610##

wherein

R.sub.a.sup.1, R.sup.3 and R.sup.4 are as defined above, or a salt thereof, to give a compound of the formula: ##STR611##

wherein

R.sup.2, R.sup.3 and R.sup.4 are as defined in claim 1, and

R.sub.a.sup.1 is as defined above, or a salt thereof, or

iii) reducing a compound of the formula: ##STR612##

wherein

R.sup.3 and R.sup.4 are as defined in claim 1, or a salt thereof, to give a compound of the formula: ##STR613##

wherein

R.sub.2, R.sub.3 and R.sub.4 are as defined in claim 1, or a salt thereof.

7. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

8. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

9. A method for the prophylactic an/or therapeutic treatment of infectious diseases caused by pathogenic microorganisms, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

Description

TECHNICAL FIELD

The present invention relates to new polypeptide compound and a salt thereof which are useful as a medicament.